American Journal of Medical Genetics 63:378–381 (1996)

Novel Findings in a Patient With Weaver or a Weaver-Like Syndrome

Gioacchino Scarano, Matteo Della Monica, Fortunato Lonardo, and Giovanni Neri

Centro di Genetica Medica, Ospedale San Giuseppe Moscati (G.S., M.D.M., F.L.), Avellino; Istituto di Genetica Medica, Università Cattolica del Sacro Cuore (G.N.), Rome, Italy

We report on a young male patient with an overgrowth syndrome, who had normal birth weight. He had a number of manifestations typical of the Weaver syndrome (WS), such as advanced bone age, peculiar craniofacial appearance, and camptodactyly. He also showed severe mental and speech retardation and demineralisation of the bones of the hands and feet. The latter can be considered as unreported manifestations of WS, or the patient could represent an example of a new WS-like syndrome.

KEY WORDS: Weaver syndrome, overgrowth, camptodactyly, advanced bone age, mental and speech retardation, bone demineralisation, new syndrome

INTRODUCTION

In 1974, Weaver et al. described a syndrome of accelerated growth, advanced bone age, distinctive craniofacial appearance, camptodactyly, and development delay, known as the Weaver-Smith or, more simply, the Weaver syndrome (WS). Major craniofacial manifestations are broad forehead, large ears, hypertelorism, prominent or long philtrum, and relative micrognathia [Cohen, 1989]. The other skeletal findings include mottled and widened distal epiphyses of femora and ulnae, scoliosis or kyphosis, and short ribs [Cole et al., 1992].

Additional findings are neurological involvement with hypotonia or hypertonia [Ardinger et al., 1986], cryptorchidism [Gemme et al., 1980; Weisswichert et al., 1981, Meinecke et al., 1983], umbilical or inguinal hernia [Cole et al., 1992], congestive cardiomyopathy [Fitch, 1980; Trabelsi et al., 1990], instability of the upper cervical spine [Muhonen et al., 1990], and nail dysplasia [Dumic et al., 1993].

With regard to heredity, most of the cases reported have been sporadic [Cole et al., 1992], although autosomal dominant [Kondo et al., 1990], autosomal dominant with sex-limited expression, or X-linked recessive [Ardinger et al., 1986], or autosomal recessive inheritance [Roussinis and Crawford, 1983], have been suggested. As a consequence, it is virtually impossible at the moment to draw any definite conclusions about the genetic cause of this syndrome [McKusick, 1994].

We report on a patient with an overgrowth syndrome that can be interpreted either as an unusual case of WS with new findings, or a novel condition.

Clinical Report

The propositus is a young male patient referred for psychomotor retardation and postnatal overgrowth. He is the fourth child of non-consanguineous parents. The mother was 34 and the father 31 years old at the time of his birth. Two sisters and one brother are healthy. Family history is negative for congenital abnormalities or mental retardation. The propositus was born spontaneously at term after an uneventful pregnancy. Birth weight was 2,900 g (10th centile), length 49 cm (25th centile), and head circumference (OFC) 35 cm (50th centile). There was a severe respiratory distress which required resuscitation.

At one year he was assessed at another hospital for psychomotor delay. On our first observation at 23 months, weight was 13.65 kg (>95th centile), height 89 cm (90th centile), OFC 49.5 cm (50th centile); and the patient presented brachycephaly, broad forehead with metopic prominence, bitemporal constriction, hypertelorism, epicanthic folds, down-slanting palpebral fissures, convergent strabismus, narrow nose, and long columella. In addition, he showed clinocamptodactyly of 5th finger bilaterally, redundant skin on dorsal aspect of fingers, prominent finger pads, short feet and toes, and bilateral retention of testes. Neurological evaluation showed muscular hypotonia with weak deep tendon reflexes and difficulty in maintaining postural position. At 4 years the propositus registered a weight of 20.4 kg (> 95th centile), height 106.5 cm (>75th centile), OFC 51 cm (>50th centile), lower segment 45 cm, U/L ratio =1.36 , hand length 13.8 cm (>97th centile), and palm 8.2 cm (>97th centile). The facial traits were

Received for publication May 3, 1995; revision received November 28, 1995.

Address reprint requests to Gioacchino Scarano, M.D., Centro di Genetica Medica, Ospedale "San Giuseppe Moscati," Via Due Principati, 83100 Avellino, Italy.

substantially unchanged with respect to the previous observation and were suggestive of the WS, with an inner canthal distance 3.3 cm (>97th centile), outer canthal distance 8.6 cm (>97th centile) (Figs. 1, 2). Also noted were hoarse cry, camptodactyly of hands (Fig. 3), partial syndactyly of toes 2–4 bilaterally, pes planus, well-developed muscular masses, advanced bone age, and marked acral demineralisation.

Dermatoglyphics were, on right, *t, abcd,* Lu W W W W; and on left, *t, abcd*, Lu Lu Lu W Lu. Also noted was a single transverse palmar-crease on right.

A metacarpophalangeal pattern profile analysis (MCPP) demonstrated the length of proximal phalanges to exceed two standard deviations above the mean (Fig. 4).

The patient could not walk unsupported and his speech and mental development were severely delayed.

He had normal parathormone, as well as plasmatic levels of calcium, phosphate, and alkaline phosphatase. No abnormalities were detected on quantitative amino acid analysis, and qualitative urinary mucopolysaccharide and oligosaccharide analysis. The complete blood count and results of liver and kidney function tests were normal. Results of an abdominal ultrasound were normal.

An MRI of the brain showed slight enlargement of lateral ventricles and persistence of cavum of septum pellucidum. An electromyography was apparently normal. A standard chromosome analysis was normal: 46,XY (RHG). The total body bone densitometry (0.745 g /cm^2) was probably normal, although normal standards for this age are not available.

Roentgenographic studies demonstrated the presence of wormian bones in the lambdoid suture, small enlargement of the iliac alae, flared distal metaphyses of femora and diffuse, and marked demineralisation of the skeleton of the hands (Fig. 5) and feet. The bone age at 23 months corresponded to 3$^{7}/_{12}$ years (>97th centile according to Tanner standards-RUS).

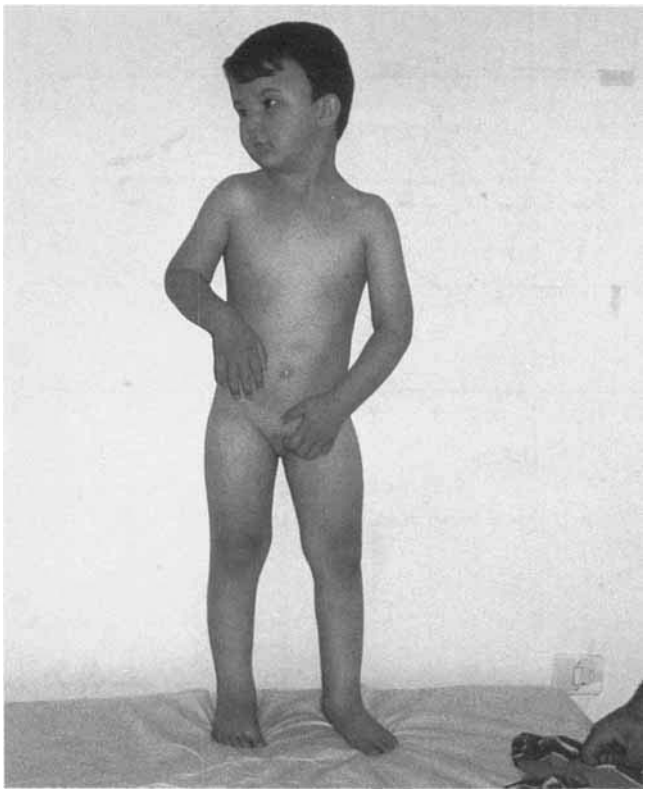

Fig. 1. Patient at 4 years.

DISCUSSION

The diagnosis of WS may be difficult in the neonatal age when there is lack of prenatal overgrowth, as in our case. Nevertheless, the finding of other characteristic abnormalities, such as typical craniofacial appearance, camptodactyly, prominent finger pads, ad-

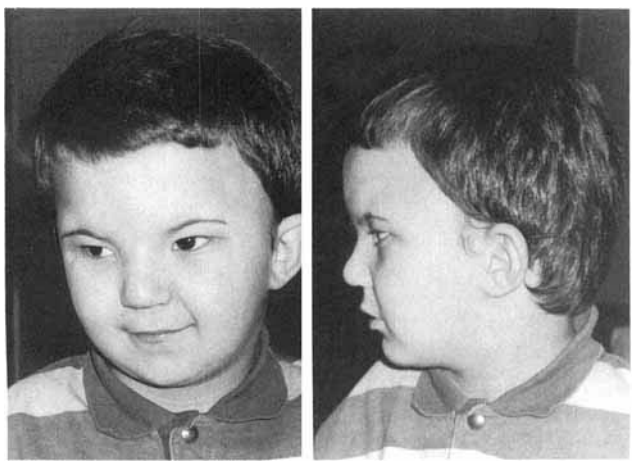

Fig. 2. Frontal and lateral view of patient at 5 years. Note the broad forehead, hypertelorism, epicanthic folds, down-slanting palpebral fissures, and long columella.

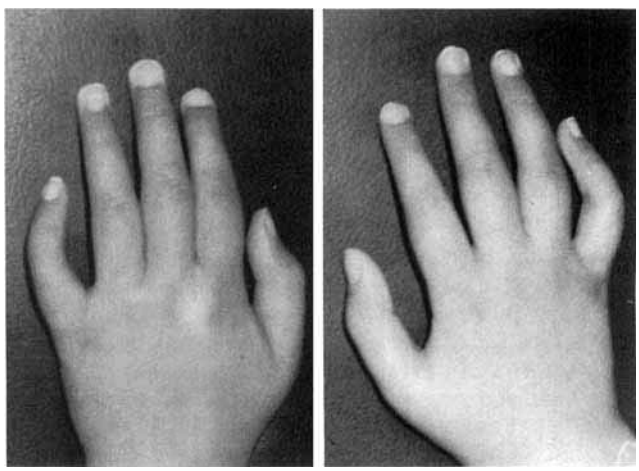

Fig. 3. Hands with clinocamptodactyly.

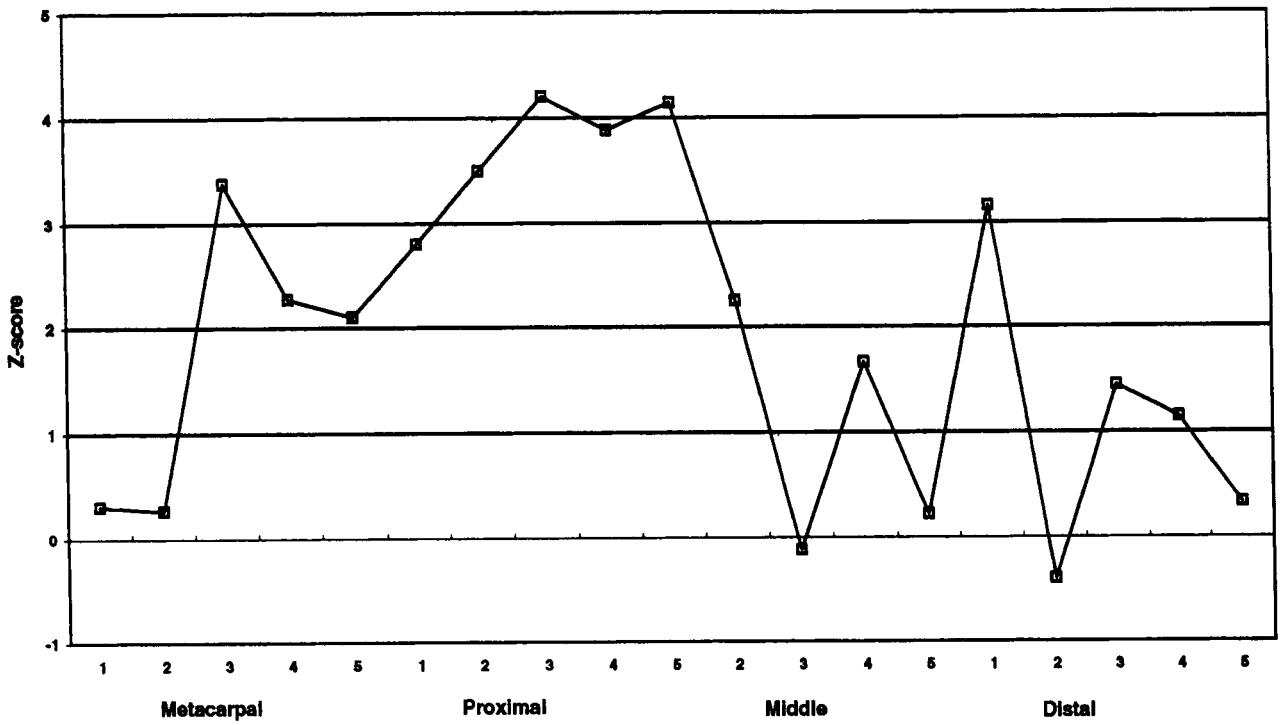

Fig. 4. MCPP of the left hand at 23 months. Note the length of proximal phalanges and first distal phalanx, which exceed two standard deviations (Z-scores).

vanced bone age, flared metaphyses, and psychomotor delay can lead to the correct diagnosis (Table I). The absence of prenatal overgrowth has already been noted in several cases of WS, previously described [Ardinger et al., 1986; Ramos Arroyo et al., 1991; Dumic et al., 1993]. Of a total of 38 cases, 11 (29%) did not show overgrowth at birth.

Achievement of overgrowth at a later stage has been explained in many cases with neonatal failure to grow due to recurrent pulmonary infections [Shimura et al., 1979], or to inadequate caloric intake [Ramos Arroyo et al., 1991].

Our patient differs from most previously reported cases of WS because of his severe developmental delay. At 4 years he does not speak, walk, or stand in the upright position and he has severe mental retardation. The only other case of WS with severe mental retardation is the patient of Ramos-Arroyo et al. [1991], a 16-month-old female, who died of generalized sepsis, congestive heart failure, and respiratory arrest. The autopsy showed cerebellar sclerosis, extensive cerebral gliosis, and vascular changes, probably representing the consequence of multiple episodes of hypoxia and electrolyte imbalance. Moreover, in many areas of the brain there were extensive neuronal losses that might have been secondary to birth trauma. The authors suggested that early neurologic deficiency led to frequent aspirations and subsequent respiratory tract infections and raised the question whether mental retardation was a primary manifestation of WS or secondary

Fig. 5. Roentgenogram of the left hand at 23 months. Note the diffuse and marked demineralisation of all bones.

TABLE I. Clinical Findings in Weaver Syndrome

Clinical findings	Patients from literature	Present patient
Excessive growth		
Postnatally	35/38	+
Prenatally	27/38	−
Performance		
Motor delay	17/18	+
Hoarse and/or low-pitched cry	20/24	+
Developmental delay or mental retardation	25/31	+
Eccessive appetite	7/11	+
Hypertonia	22/34	−
Hypotonia	5/24	+
Seizures	3/22	−
Craniofacial		
Micrognathia	32/33	−
Ocular hypertelorism	32/35	+
Large ears	31/34	−
Increased bifrontal diameter	29/31	+
Telecanthus	18/19	−
Long and accentuated philtrum	25/31	−
Macrocephaly	25/30	−
Dysplastic ears	8/16	−
Strabismus	5/11	+
Depressed nasal bridge	13/26	+
Down-slanting palpebral fissures	7/19	+
Flat occiput	7/17	+
Epicanthic folds	3/16	+
Extremities		
Prominent finger pads	18/22	+
Deeply set, narrow or hyperconvexed nails	17/22	−
Limited extension of ankles, wrists, hips, or knees	12/15	+
Broad thumbs	7/11	−
Hyperextensibility of fingers	7/9	−
Camptodactyly	18/22	+
Talipes equinovarus	9/15	−
Skeleton		
Increased bone age	26/28	+
Flared metaphyses, especially of distal femora and ulnae	27/32	+
Advanced general osseous maturation	25/29	+
Acral demineralisation	?	+
Mottled or irregular epiphyses	5/10	−
Scoliosis or kyphosis	5/12	−
Atlantoaxial instability	1/38	−
Short ribs	2/7	−
Other		
Umbilical hernia	16/19	−
Inguinal hernia	9/10	−
Excessive and loose skin of the neck or extremities	18/21	+
Cryptorchidism	6/10	+
Excessive or prolonged hyperbilirubinemia	3/5	−
Hyperydrosis of palms/soles	3/38	−
Congestive cardioymiopathy	1/38	−
Mitral valve prolapse	1/38	−

to central nervous system damage [Ramos-Arroyo et al., 1991].

Our patient actually had a severe respiratory distress at birth, although a cerebral MRI at 4 years showed only modest ventricular widening and the persistence of the cavum septi pelluci. Except for the cases in which the developmental status is not specified, all other published patients have borderline or mild mental handicaps. The behavioural problems may reflect the patient's frustration, when communication is a problem, rather than an intrinsic component of the syndrome [Cole et al., 1992]. In addition to the known manifestations of WS, our patient presents a previously unreported finding, namely, an acral bone demineralisation, whose origin is presently unknown. It could be related to the accelerated osseous maturation, which may cause disharmonic carpal and tarsal bone development, [Ramos-Arroyo et al., 1991].

Because this patient is not a typical case of WS with respect to physical phenotype, psychomotor development, and presence of a previouly unreported finding (acral bone demineralisation), it remains a matter of debate whether it can be considered a bona fide WS case or an example of a new, similar condition.

The question will eventually be answered by the cloning of a WS gene. Meanwhile, we think it is important to report new patients as candidates for future molecular tests.

REFERENCES

Ardinger HH, Hanson JW, Harrod MJE, Cohen MM, Tibbles JAR, Welch JP, Young-Wee T, Sommer A, Goldberg R, Shprintzen RJ, Sidoti EJ, Leictman LG, Hoyme HE (1986): Further delineation of Weaver syndrome. J Pediatr 108:228–235.

Cohen MM (1989): A comprehensive and critical assessment of overgrowth and overgrowth syndromes. In Harris H, Hirshhorn K (eds): "Advances in Human Genetics 18". New York and London: Plenum Press, pp. 181–303.

Cole TRP, Dennis NR, Hughes HE (1992): Weaver syndrome. J Med Genet 29:332–337.

Dumic M, Vukovic J, Cvitkovic M, Medica I (1993): Twins and their mildly affected mother with Weaver syndrome. Clin Genet 44:338–440.

Fitch N (1980): The syndromes of Marshall and Weaver. J Med Genet 17:174–178.

Gemme G, Bonioli E, Ruffa G, Lagorio V, (1980): The Weaver-Smith syndrome. J Pediatr 97:962–964.

Kondo I, Mori Y, Kuwajima K (1990): A japanese male infant with the Weaver syndrome. Jpn J Human Genet 35:257–262.

McKusick VA (1994): "Mendelian Inheritance in Man. A Catalog of Human Genes and Genetic Disorders." Baltimore and London: The Johns Hopkins University Press.

Meniecke P, Schaefer E, Engelbrecht R (1983): The Weaver syndrome in a girl. Eur J Pediatr 141:58–59.

Muhonen MG, Menezes AH (1990): Weaver syndromes and instability of the upper cervical spine. J Pediatr 116:596–599.

Ramos-Arroyo MA, Weaver DD, Banks ER (1991): Weaver Syndrome: a case without early overgrowth and review of the literature. Pediatrics 88:1106–1111.

Roussinis SH, Crawford MJ (1983): Siblings with Weaver syndrome. J Pediatr 102:595–597.

Shimura T, Utsumi Y, Fujikawa S, Nakamura H, Baba K (1979): Marshall-Smith syndrome with large bifrontal diameter, broad distal femora, camptodactyly, and without broad middle phalanges. J Pediatr 94:93-95.

Trabelsi M, Ben Hariz M, Monastiri K, Taktak M, Bennaceur B (1990): Weaver's syndrome. A propos of a new case. Ann Pediatr 37:327–330.

Weaver DD, Graham CB, Thomas IT, Smith DT (1974): A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J Pediatr 84:547–552.

Weisswichert PH, Knapp G, Willich E (1981): Accelerated bone maturation syndrome of the Weaver type. Eur J Pediatr 137:329–333.